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# Women and HIV Infection: The Makings of a Midlife Crisis

**Nanette Santoro, MD**[a,b], **Maria Fan, BS**[a], **BatSheva Maslow, MD**[a], and **Ellie Schoenbaum, MD**[b,c]

[a]Departments of Obstetrics, Gynecology & Women's Health, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY, 10461 USA

[b]Department of Medicine, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY, 10461 USA

[c]Department of Epidemiology and Population Health, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY, 10461 USA

## Abstract

With the advent of highly active antiretroviral agents, women with HIV infection can expect to live longer than ever before. This increased survival has led to concerns about the long-term implications of HIV disease and its treatment. Women with HIV infection appear to lose ovarian function earlier in life than women without HIV infection. They also have evidence of reduced bone mineral density and increased cardiovascular risk. Moreover, many of these increases in risk factors are present even prior to the menopausal transition. All of these risks, present at mid-life, augur poorly for future health and describe a substantially increased burden of disease likely to accrue to HIV infected women as they enter older age groups. Further compounding the adversity faced by the HIV infected, the demographics of women most vulnerable to this disease include adverse social and economic influences, both of which worsen their long term prognosis. For example, drug use and poverty are related to more severe menopausal symptoms and chronic stress is related to worse psychological and cardiovascular risk. An understanding of how menopause interacts with HIV infection is therefore most important to alert the clinician to perform surveillance for common health problems in postmenopausal women, and to address directly and appropriately symptomatology during the menopausal transition.

### Keywords

HIV; menopause; women; diabetes; heart disease; symptoms

## 1. Introduction

While the health care community can rejoice in the decrease in both lethality and new cases of HIV infection and an increased ability to treat HIV with highly active antiretroviral therapy, there are new concerns that must be addressed (1). Although deaths from AIDS were observed



Corresponding author: Nanette Santoro, MD, Professor and Director, Division of Reproductive Endocrinology & Infertility, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Mazer 314, Bronx, NY 10461, USA, 718-430-3152 phone, 718-430-8586 FAX, glicktoro@aol.com.

to decline, HIV-related cancer, liver disease, cardiovascular disease and suicide were all observed to increase from 2000–2005 in the French national Mortalite survey(2)—a striking reminder of how quickly the epidemic has matured in developed countries. Women who acquired HIV in the second decade of life or afterwards are now approaching or have completed the menopausal transition. Over the short term, the menopausal transition represents a source of stress for many women, with a transient worsening of sleep and mood, and an increased likelihood of vasomotor symptoms and bothersome sexual dysfunction(3). Over the long term, menopause brings with it an increased concern about the acquisition of chronic diseases of aging: cardiovascular disease, type 2 diabetes mellitus (T2DM), osteoporosis, cognitive impairment and an overall increased risk of many types of cancer. Women and their health care providers work together to detect the more common, serious and chronic diseases early, and to pinpoint and address risk factors.

The challenge of identifying vulnerabilities, screening appropriately, and taking steps to prevent or delay chronic illness is amplified in the aging woman with HIV infection. Evidence is accruing that HIV infected women are at heightened risk for virtually all of the above-mentioned diseases of aging, and that they enter the menopause with a substantially increased risk factor burden. There is therefore ample reason to believe that HIV infected women will acquire disease early and that it will be more severe. This review will highlight the available data that bear on this topic to help identify the scope of the issue and help direct the clinician appropriately.

## 2. Findings

### 2.1 Do HIV-Infected Women Have an Earlier Menopause?

To the extent that menopause exacerbates the risks of diseases of aging, it is important to consider whether natural menopause occurs earlier in HIV-infected women. It is not a simple question to ask, because the data on HIV infected populations is usually confounded with other risk factors for early menopause, as well as risk factors for irregular menses. The earlier presence of irregular menses in HIV infected women may not be assumed to be due to menopause, since hypothalamic amenorrhea may be present.

Several investigators have studied the effect of HIV on the age at which women reach menopause. Significant reductions in the average age at menopause have been observed in some study populations (4–6). Schoenbaum, et al, found that HIV-infected women had menopause at a median age of 46 years, as compared to a median age at menopause of 47 years in HIV-uninfected women from the same cohort(5). This finding underscores the importance utilizing comparable control groups, as the women in both groups within the Schoenbaum cohort were highly enriched in risk factors for early menopause, such as cigarette smoking (7). Others have found comparable mean ages but a disproportionate number of HIV+ women reaching menopause extremely early(6,8,9). Still others have found no significant distinction in the age at which HIV+ women reach menopause(9,10). A variety of additional factors have been implicated in causing earlier menopause, including smoking, drug use, and psychosocial stress, all of which are common among many HIV infected populations(7).

In one cohort study in which blood sampling was performed to assess reproductive hormones, some associations were observed between use of highly active antiretroviral drugs (HAART) and elevated LH and FSH(11). Cocaine use was associated with lower estradiol in this sample, indicating a possible ovary-toxic effect of this street drug. Opiate use was associated with lower LH and FSH, indicating inhibition of central neural reproductive drive and a tendency towards amenorrhea in this group, in the absence of menopause or evidence of loss of ovarian reserve. Thus, interpretation of menstrual cycle patterns in HIV infected women should be done with caution, as not all menstrual irregularities can be attributed to menopause.

### 2.2 Insulin Resistance and Diabetes—Their Linkage to HAART and Hepatitis C

While people have been living longer with HAART, it has also been associated with an increase in metabolic disturbances. A number of studies have pointed to possible detrimental effects of both HIV infection and HAART on glucose metabolism and insulin resistance, and their linkage to the development of T2DM or the metabolic syndrome. HCV coinfection also has been examined as a possible modifier of development of metabolic abnormality.

Butt et al analyzed baseline prevalence and associated risk factors for type 2 diabetes in the Veterans Aging Cohort Study (VACS)—a predominately male population(12). The study included 3227 HIV-infected and 3240 HIV-uninfected veterans. The HIV-infected participants were younger, more likely to be African-American, more likely to report drug use and to be HCV coinfected, and of lower BMI than the HIV uninfected participants. The HIV-infected participants in this study had a significantly lower prevalence of T2DM (14.9% versus 21.4%, $P < 0.0001$), likely driven by the lower BMI in the HIV-infected individuals. Multivariate logistic regression showed that HIV-infected participants had lower odds of T2DM (odds ratio 0.84; 95% CI 0.72–0.97). Increasing age, black or Hispanic race, increasing BMI, and HCV co-infection were all associated with T2DM in HIV-infected individuals. Increasing age and BMI were also associated with increased odds of diabetes in HIV-uninfected individuals, but the effect was more pronounced in HIV-infected individuals. No association was found between HIV RNA levels and diabetes mellitus. HCV co-infection was not associated with T2DM in HIV-uninfected participants. Nucleoside reverse transcriptase inhibitor (NRTI) and non-nucleoside reverse transcriptase inhibitor (NNRTI) but not PI use were associated with increased odds of diabetes. In contrast, moderate to frequent alcohol use was associated with decreased odds of developing T2DM. Increasing age, minority race and obesity are traditional risk factors for diabetes, but these data imply that some of these traditional risk factors have a larger effect size in HIV infected individuals, and additional factors such as HCV co-infection and HAART use are also important to consider (12). Some limitations of this study to keep in mind include its evaluation of prevalence, not incidence, and the lack of determination of a family history of diabetes.

Brar et al. examined baseline prevalence of diabetes mellitus and associated factors in 2565 HIV-infected individuals aged 20–59, who were naïve to antiretroviral therapy(13). The sample was draw from community sites throughout the US, and was 23% female. Findings were compared to 6585 non-infected controls from the National Health and Nutritional Examination Survey (NHANES) (13). The HIV-infected cohort differed significantly from the NHANES cohort in having lower mean BMI and a higher proportion of hepatitis C seropositivity, injection drug use, and men who have sex with men. African-American or Latino ethnicity, increasing age, and higher BMI were all associated with increased prevalence of diabetes in both HIV-infected and NHANES controls (13). After adjustment for these factors, there was not a significant difference in diabetes prevalence between HIV-infected patients and NHANES controls in the overall sample (P=0.58) (13). When considering women only, older age and higher BMI were significantly associated with diabetes in both HIV-infected and NHANES controls. Female sex was significantly associated with diabetes in HIV-infected patients (OR=2.30; 95% CI: 1.47–3.60) but not among the NHANES population. The investigators concluded that there was not an increased prevalence of T2DM in antiretroviral-naïve HIV-infected individuals. As in the prior study, traditional risk factors for diabetes appeared to be the most important predictors.

Tien et al. examined the incidence of T2DM in 1524 HIV-infected and 564 HIV-uninfected women in the Women's Interagency HIV Study (WIHS)(14). Diabetes was defined as fasting glucose ≥1.26 mg/L or report of anti-diabetic medication or DM diagnosis (subsequently confirmed)(14). They found no significant difference in T2DM incidence in HIV-infected women compared to HIV-uninfected women (14). With regards to antiretroviral therapy, only

cumulative nucleoside analog reverse transcriptase inhibitor (NRTI) use for greater than three years was significantly associated with an increased risk of T2DM (relative hazard 2.64; 95% CI 1.11–6.32) (14).

Tien et al. also carried out homeostasis model assessments (HOMA) to assess insulin resistance in 1614 HIV-infected and 604 HIV-uninfected participants from the Women's Interagency HIV Study (WIHS)(15). The HIV-infected women were older, with lower BMI and hip size, but more likely to be HCV-infected and postmenopausal than HIV-uninfected women(15). HIV-infected women also had higher a HOMA ratio (2.19 vs. 1.83; P<0.001) (15). They found higher median HOMA in HIV-infected women reporting use of both PI-containing HAART (1.20; 95% CI 1.11– 1.30) and non-PI containing HAART (1.10; 95% CI 1.01–1.20) compared to HIV-uninfected women (15). Additional factors associated with higher HOMA included cumulative exposure to NRTIs for greater than three years, Hispanic race, Hepatitis C seropositivity, higher BMI and more advanced menopausal status. In particular, more than 1 year's exposure to the NRTI stavudine was associated with higher HOMA, with each additional year accounting for a 6% increase in median HOMA (95% CI 1.01–1.11). Cumulative exposure to NRTIs, proease inhibitors (PIs), or the individual NRTIs lamivudine, zidovudine, abacavir, or tenofovir were not associated with HOMA. Similar relationships have been noted by others (16).

Other studies have implicated hepatitis C as playing a role in the development of T2DM(17). In the MS HIV cohort, hepatitis C seropositivity was related to insulin resistance and associated with an increased risk of T2DM, but only among obese women(18).

### 2.3 Cardiovascular Disease—Evidence for Increased Risk

Traditional cardiovascular risk factors such as serum lipoproteins, are increased in HIV infected women. HIV infection is associated with higher triglycerides and lower HDL cholesterol. Obese women with HIV infection also demonstrated higher total cholesterol and LDL, as did women with HIV infection who were taking HAART (19). Interestingly, in this cohort study, higher CD4 counts were also associated with increased total and LDL cholesterol as well as increased apolipopotein-B (Apo B). In a recent study of 145 HIV-infected Thai patients, 62% of whom were female, HIV RNA was associated with increased inflammatory markers soluble vascular cell adhesion molecule-1 (sVCAM-1) and chemokine ligand 2. Thus, both traditional and newer, soluble markers of inflammation appear to be elevated in HIV-infected individuals.

Other markers of cardiovascular health appear to be altered in HIV infected individuals, sometimes related to treatment or stage of disease. Carotid intimal medial thickness has been observed to be increased in HIV infected women and men(20), and in one study, in association with low CD4 cell counts(21). Microvascular responses to cold stress are impaired in HIV infected men and women(22). Similarly, peripheral arterial disease as measured by an ankle-brachial index, was worse in 99 HIV infected individuals compared to 99 age and sex matched uninfected individuals(23).

Aortic stiffness was measured using pulse wave velocity (PWV) in a small group of 39 untreated, HIV infected men and women and compared to 78 age and sex matched uninfected individuals(24). HIV patients had a higher aortic PWV (7.5+/−1.4 versus 6.7+/−1.1 m.s(−1); P=0.001) than control subjects, and HIV infection was an independent risk factor for increased aortic stiffness. Taken together, the data indicate a substantial increase in cardiovascular disease risk burden in HIV infected women, regardless of treatment status.

### 2.4 Menopausal Symptoms—Earlier Appearance, Greater Intensity in HIV-Infected Women

Common symptoms of menopause, such as vasomotor symptoms, vaginal dryness and dsypareunia, and adverse mood have been evaluated in relation to HIV infection. In the MS-HIV cohort study, 536 women, 37% of whom were defined as perimenopausal, were evaluated for symptoms(25). 89% of women reported psychological symptoms, primarily depressive symptoms, 63% reported arthralgia and 61% reported vasomotor symptoms. Perimenopausal women, HIV-infected women and women with high depressive symptom reporting were all more likely to report menopausal symptoms, and symptom reporting was linearly related to stressful life events. Ferreira, et al, found similarly increased psychological and vasomotor symptoms among 96 Brazilian HIV-infected women compared to uninfected women, with an overall 1.65 fold increased risk of symptoms among the HIV infected(26). In another study of 120 primarily African-American women, an 80% prevalence of hot flashes was observed, among HIV infected women compared to 38–69% in the general population(9). Cocaine use was associated with more frequent reporting of vaginal dryness in this study(9). HIV-infected women appear to have more symptoms, but there is also evidence that symptoms of menopause may be incorrectly attributed to another process, such as worsening of HIV disease or drug withdrawal(27).

### 2.5 Osteoporosis and Osteopenia—Early Onset and Worse Trajectory

An increased prevalence of low bone mineral density (BMD) has been consistently found among HIV+ individuals. Menopausal HIV infected women appear to be at exceptional risk. Dolan et al. compared the BMD of eighty-four HIV infected women with that of sixty-three age matched controls(28). Osteopenia was present in 54% of HIV infected women compared to 30% of uninfected controls. Osteoporosis was present in 10% of HIV infected women compared with only 5% of controls. Within the HIV infected study group, BMD was significantly reduced among women with oligomenorrhea or with an FSH>15.

Yin et al. studied 40 HIV infected women older than 50 years with greater than one year of amenorrhea(29). Compared to age-matched controls, 42% of HIV infected women had lumbar spine osteoporosis versus 23% of uninfected controls. Hip osteoporosis was observed in 10% of HIV infected women compared to 1% of controls.

The MS-HIV Study examined BMD in 495 women, of whom 53% were HIV+(30). Compared to national estimates for middle-aged women, low bone density was more prevalent in the study population. 27% of HIV infected women were osteopenic compared to 19% of uninfected controls. HIV infection was independently associated with low BMD only among non-black participants.

The etiology behind the accelerated bone loss in HIV infected women is still unclear and likely to be multifactorial. Chronic T-cell activation found in HIV infected individuals promotes bone resorption via pro-inflammatory cytokines, such as TNF-α, IL-6 and IL-1(29). Secondary effects of HIV infection such as weight loss, hypoparathyroidism and vitamin D deficiency likely play a role as well. While protease inhibitors have been implicated in the acceleration of bone loss in HIV patients, in the above studies, bone loss was similar among HAART and non-HAART users (29,30). Teichman et al. demonstrated significant bone loss in HAART naïve participants as compared to age matched controls (31).

Estrogen deficiency with the onset of menopause can be expected to exacerbate HIV-associated bone-loss. With loss of estrogen at menopause, HIV+ women become exposed to higher levels of bone resorbing cytokines, lending to a rapid rate of bone loss(29). Given the evidence of increased susceptibility to fracture with decreasing bone density, treatment of HIV-infected menopausal women should be geared towards fracture prevention. Educating HIV+ middle-

aged women regarding their risk of fracture and the need for calcium and vitamin D supplementation is crucial. Early screening of this population may be prudent given the propensity for earlier menopause as well as dramatic perimenopausal bone loss. Early treatment with a bisphosphonate has been shown to be effective in treating HIV-associated bone loss (32) and is likely an underutilized therapeutic option in this population.

### 2.6 Malignancy

Aging increases the risk of cancers of many types, and HIV infection exacerbates this risk. Similar to other diseases, HIV-infected populations tend to be enriched in risk factors for cancer. Cigarette smoking is highly prevalent in many HIV cohorts, and lung cancer is one of the most common non-HIV related cancers related to mortality across several studies(2,33). Other cancers more common in HIV infected individuals include non-Hodgkin's lymphoma (34) and multiple myeloma (35). Cervical cancer risk is known to be greater in HIV-infected women, and they are at lifelong risk for increased cervical screening anomalies(36,37). Despite this known risk, cervical cancer screening remains suboptimal in this population(38). Interestingly, recent findings implicate hypovitaminosis A as a potentially correctable etiology for increased cervical cancer in this population (39).

### 2.7 Cognition—Concerns for a Group at Excess Background Risk

Age and menopause related declines in cognition are a subject of great controversy. Although high hopes were implied for postmenopausal therapy as a means to reduce age related dementia, the Women's Health Initiative clinical trials did not support such a notion(40). However, aspects of verbal memory and executive function may be improved by hormones(41,42). This is an issue of critical importance to women who are infected with HIV, since they are already highly vulnerable to HIV related neurocognitive impairment(43). There is an urgent need to begin to address these issues in the aging female, HIV-infected population.

## 3. Conclusions

It is too early to declare victory on the war against HIV and AIDS. As better treatments have been forthcoming, it is vital that the clinicians who care for HIV infected women shift their orientation from an acute to a chronic focus. There is clear evidence from numerous studies that women infected with HIV are vulnerable to worse menopausal symptoms, increased risks of T2DM, cardiovascular disease, osteoporosis, cancer, and neurocognitive impairment. All of these conditions require surveillance and many of them can be prevented or delayed in onset by using behavioral strategies. Menopausal HIV infected women should be encouraged to optimize their cardiovascular health, maintain their weight within the normal range, stop smoking, and adhere to osteoporosis and cancer screening guidelines as appropriate. It is too early to know whether hormone therapy will pose a net benefit to HIV infected women, but over the short term, treatment of menopausal symptoms, be it hormonal or non-hormonal, is likely to be indicated.

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